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Bureau of Epidemiology

Jennifer G. Brown, JD, MS
Bureau Director

October 2, 2012

Dear Colleagues:

As discussed at the last TB Advisory Committee, the Utah Department of Health, Tuberculosis Program, has developed a protocol for the new 12-week, once weekly INH and Rifapentine (RPT) regimen for treating LTBI. Although controlled studies have proven this to be a safe alternative to the standard 6-9 months of INH, it is still new to the mass market. This is why we, like many other states, are proceeding with caution, and are advising strict adherence to recommended procedure.

Please review the accompanying attachments, and feel free to contact me with any questions. As noted in the protocol, at this time our stock will only be available for the following patients: exposed contacts to a sputum smear positive case, newly arrived refugees, or HIV+ individuals. Please forward a copy of the prescription with your request for state supply. You are, of course, free to offer this regimen to others who fall within guidelines; but at the patient's expense.

Sincerely,

Larry Nilet, RN
TB Nurse Consultant
Utah Department of Health/TB Control Program
801-538-9906

UTAH DEPARTMENT OF HEALTH (UDOH) GUIDANCE FOR THE MANAGEMENT OF PERSONS ON TREATMENT FOR LATENT TUBERCULOSIS (TB) INFECTION (LTBI) WITH ISONIAZID (INH) AND RIFAPENTINE (RPT) BY DOT, WEEKLY FOR 12 WEEKS

1. On December 9, 2011, The Centers for Disease Control and Prevention published the following article in the Morbidity and Mortality Weekly Report, Vol. 60, No. 48, pp. 1650-1653: **Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection.**
2. On October 1, 2012 our state TB physician consultants recommended, with caution, the implementation of the CDC use of the INH-RPT regimen for LTBI, using directly observed therapy (DOT) for 12 weeks.
3. UDOH recommends the use of the 12 weeks directly observed therapy INH-RPT regimen for LTBI for persons age 12 or older (except as outlined in paragraph E) who are otherwise healthy and meet the following criteria:
   A. Contacts with LTBI, with recent exposure to sputum smear positive TB.
   B. Documented conversions of Tuberculin Skin Test (TST) or Interferon-Gamma Release Assay (IGRA).
   C. Individuals with a predictive factor for greater likelihood of developing TB and risk factors for not completing 9 months of INH therapy.
   D. Radiographic findings of healed pulmonary TB after a diagnosis of TB disease has been definitively ruled out.
   E. Persons 2-11 years of age only if the risk of progression to TB disease is great or highly likely and the completion of nine months of INH is unlikely. The preferred regimen for children aged 2-11 years is nine months of daily INH. The number of children in this age range who have received INH-RPT is insufficient for assessing tolerability and efficacy. However, INH-RPT can be considered on a case-by-case basis when both 1) the circumstances make the completion of 9 months of daily INH unlikely and 2) the likelihood or the hazard of TB is great (e.g., recent *M. tuberculosis* infection in a preschool child).
   F. Persons diagnosed with LTBI who are HIV +, otherwise healthy, and not on anti-retroviral therapy. Anti-retroviral therapy should not be delayed just to give INH and RPT. If anti-retroviral therapy is to be started, give an alternative LTBI regimen that does not include a rifamycin drug, such as INH for 9 months.
4. Treatment using state-purchased medication may be used for the following high-priority groups:
   A. Exposed contacts to a sputum smear positive case;
   B. Newly arrived refugees;
   C. HIV+ individuals.
5. **This drug regimen is contraindicated for and is not recommended for the following persons:**
   A. Children under 2 years of age.
   B. Persons who have HIV/AIDS and are on anti-retroviral therapy.
   C. Women who are pregnant or likely to become pregnant during the 12 weeks of therapy and those who are sexually active and do not agree to use a barrier method of contraception in place of/addition to hormonal agents.

D. Contacts to cases who are resistant to INH and/or the rifamycins (rifampin, rifapentine, rifabutin).
E. TB suspects or cases.
F. Persons on medications which should only be used after consideration of the drug-drug interactions with rifapentine, especially those drugs that follow the cytochrome p450 pathway, and for whom careful monitoring can be provided include:
    1. Warfarin sodium (Coumadin),
    2. Dilantin,
    3. Phenobarbital,
    4. Psychotropic drugs,
    5. Methadone,
    6. Disulfuram (Antabuse),
    7. Chemotherapy Agents,
    8. Other drugs also known to carry the same warning with Rifampin.

6. Baseline assessment of clients for this regimen includes:
    A. Health history, including medications (prescription and non-prescription medications and herbal supplements) the patient is taking, social history, medical history, TB history, and signs and symptoms of TB.
    B. Temperature, weight and blood pressure at baseline.
    C. Document date of last menstrual period for women of child bearing age
        1. If a woman is taking Depo-Provera injections for contraception, she may not have menstrual periods. Assess for date of last Depo-Provera injection.
    D. Document the birth control methodology for all potentially sexually active females:
        1. If pregnancy is suspected, draw a serum pregnancy test and delay start of medication until a negative test result is received. If the serum pregnancy test result is positive, this patient cannot take the INH-RPT regimen; it is contraindicated in pregnancy.
    E. Obtain liver function test (including AST, ALT and total bilirubin) and CBC with platelets with:
        1. HIV infection,
        2. Liver disorders, including hepatitis B and C, cirrhosis,
        3. In the immediate postpartum period (less than or equal to 3 months after delivery),
        4. Regular alcohol usage or alcohol abuse,
        5. Older patients (35 or older), especially those taking medications for chronic medical conditions,
        6. Patients of any age taking medications that are potentially hepatotoxic,
        7. Persons with diabetes.
        8. Persons with blood dyscrasia-causing conditions.
    F. Monitor the CBC with platelets test results for evidence of neutropenia and thrombocytopenia; if found, refer for medical evaluation.

G. Refer for medical evaluation if the baseline liver function tests and/or the CBC with platelets are elevated or the platelet level is less than 100,000.

H. If the baseline CBC with platelets and/or baseline liver function tests are abnormal, delay the start of treatment until authorized by the physician.

I HIV test based on risk assessment.

J. A woman who is within the three month post-partum period must have careful laboratory and clinical monitoring. Draw liver function tests and a CBC with platelets at baseline and every month during treatment. Ensure the clinical monitoring listed in section 8 of this standing delegation order is done with every dose and monthly.

7. Treatment is by DOT only. DOT assessment and observation by video technology or enhanced self-administered therapy are **NOT** to be used with this regimen.

A. Each medicine dosage is calculated by body weight:

Isoniazid
15 mg/kg rounded up to nearest 50 or 100 mg; 900 mg maximum
Rifapentine
10.0 – 14.0 kg = 300 mg
14.1 – 25.0 kg = 450 mg
25.1 – 32.0 kg = 600 mg
32.1 – 49.9 kg = 750 mg
50 kg or greater = 900 mg maximum

Isoniazid is formulated as 100 mg and 300 mg tablets. Rifapentine is formulated as 150 mg tablets packed in blister packs that should be kept sealed until usage. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

B. Review s/s medication side effects (see 8B) and s/s active TB before start of treatment and each dose, and complete DOT log. If any are reported, notify PHN before dosing. (An RN or MD should review the above with the patient before initiating regimen.)

C. Completion of treatment is defined as 12 doses taken in 16 weeks. Each dose must be separated by at least 72 hours. Only in extreme circumstances should this period be reduced to less than weekly dosing; for example, to prevent a patient from missing a dose. Do not shorten the dosing interval on a routine basis.

D. At the beginning of treatment, obtain enough medication for the entire 12 doses for each patient before starting treatment, to avoid treatment interruption due to drug supply problems.

E. Give pyridoxine, 50 mg/week to
1. Persons with diet deficient in vitamin B6
2. Persons who abuse alcohol
3. Patients with diabetes

F. If diagnosed with LTBI and HIV at the same time, work with the HIV provider to make a decision whether to start HAART or INH/RPT, or another LTBI treatment regimen. Anti-retroviral therapy should not be delayed to give INH and RPT. If

anti-retroviral therapy is to begin, give another LTBI treatment regimen that does not conflict with the anti-retroviral therapy. Get an expert medical consultation if needed to determine which therapeutic regimen to give with anti-retroviral therapy.

G. The assessment and initial dose of INH and RPT is to be given by a registered nurse.

8. Monitoring

A. At every DOT visit, ask all questions on the DOT Log. If the patient answers yes to any symptom, the DOT worker must call the TB nurse for instructions about whether to give the medication.

B. At each encounter, patients should be instructed in their preferred language to call their nurse immediately if they have fever, yellow eyes or skin, dizziness, rash, aches, bleeding gums, easy bruising, mouth sores, or more than one day of nausea, vomiting, weakness, abdominal pain, or loss of appetite. On weekends or holidays the patient should seek immediate medical attention. INH-RPT should be withheld while the cause of symptoms is being determined.

C. At least monthly, patients should undergo a clinical assessment, including inquiries about side effects and s/s active TB and a targeted physical examination (see D below). Any abnormalities should be discussed with state (or your) physician consultant. Meds should be stopped pending physician consult.

D. The physical examination should include vital signs (temperature, weight and blood pressure), inspection of the skin and eyes for jaundice and the mouth for lesions, assessment for rash, and palpation of the abdomen for signs of abdominal/liver tenderness.

E. Subsequent liver function tests (including ALT, AST and total bilirubin) and/or CBC with platelets should be drawn monthly for:

1. Patients whose baseline or subsequent testing is abnormal.
2. Patients at risk for/hx of liver disease.
3. Hx blood dyscrasias.
4. HIV infection.
5. Patients within the three month postpartum period.
6. Regular alcohol use or alcohol abuse.

F. Discontinue INH-RPT if a serum aminotransferase concentration is greater than or equal to five times the upper limit of normal even in the absence of symptoms or greater than or equal to three times the upper limit of normal in the presence of symptoms. Refer for medical care and consult the physician for the patient's plan of care. **Do not restart the regimen without a new physician's order.**

G. Document the date of a woman's last menstrual period monthly at the clinical assessment visit. If the patient becomes pregnant during treatment with INH-RPT, discontinue this regimen. Remember if a woman is taking Depo-Provera injections for contraception, she may not have menstrual periods. Assess the date of last Depo-Provera injection and the date that the next injection is scheduled. If a women's menstrual period is >3 days late, hold the INH and RPT and check a serum pregnancy test. Do not restart medications unless the pregnancy test is negative.

H. Report severe adverse drug effects to UDOH TB Nurse Consultant, 801-538-9906.

1. Adverse reactions resulting in hospitalization or death should be reported to the CDC Division of Tuberculosis Elimination at 404-639-8401 or LTBIdrugevents@cdc.gov
2. Adverse events or medication errors also should be reported to FDA MedWatch at http://www.fda.gov/medwatch, by submitting a MedWatch Form 3500 (available at http://www.fds.gov/medwatch/safety/FDA-3500_fillable.pdf) or by calling 1-800-FDA-1088.

References

Jereb, J. A., et al. "Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection". Morbidity and Mortality Weekly Report 60:48, December 9, 2011, 1651-1653. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_e%0d%0a

Pugh, Maureen Barlow (Ed., et al). Stedman's Medical Dictionary, 27th Edition. Philadelphia: Lippincott, Williams & Wilkins, 2000.

Centers for Disease Control and Prevention "Treatment Options for Latent Tuberculosis Infection." http://www.cdc.gov/tb/publications/factsheets/treatment/LTBItreatmentoptions.htm

UTAH DEPARTMENT OF HEALTH DIRECTLY OBSERVED THERAPY LOG
12-Dose Isoniazid-Rifapentine Latent TB Infection Treatment

Patient Name: _____ **Date of Birth:** _____
Initial Weight: _____**kg** **Dose:** _____mg **INH**_____mg **RPT**

Date: Dose:	__/__ __1__	__/__ __2__	__/__ __3__	__/__ __4__	__/__ __5__	__/__ __6__	__/__ __7__	__/__ __8__	__/__ __9__	__/__ __10__	__/__ __11__	__/__ __12__
Loss of appetite	□	□	□	□	□	□	□	□	□	□	□	□
Nausea or vomiting	□	□	□	□	□	□	□	□	□	□	□	□
Yellow eyes or skin	□	□	□	□	□	□	□	□	□	□	□	□
Diarrhea	□	□	□	□	□	□	□	□	□	□	□	□
Rash or hives	□	□	□	□	□	□	□	□	□	□	□	□
Fever or chills	□	□	□	□	□	□	□	□	□	□	□	□
Sore muscles	□	□	□	□	□	□	□	□	□	□	□	□
Numbness or tingling	□	□	□	□	□	□	□	□	□	□	□	□
Methadone withdrawal*	□	□	□	□	□	□	□	□	□	□	□	□
Dizziness/lightheaded	□	□	□	□	□	□	□	□	□	□	□	□
Unusual bleeding/bruising	□	□	□	□	□	□	□	□	□	□	□	□
Rx stop or held	□	□	□	□	□	□	□	□	□	□	□	□
No adverse reaction	□	□	□	□	□	□	□	□	□	□	□	□
Current Weight	kg	kg	kg	kg	kg	kg	kg	kg	kg	kg	kg	kg
Blood Pressure	/	/	/	/	/	/	/	/	/	/	/	/
HCW Initials**												

* (≥ 3 new symptoms for ≥ 7 days) nausea and vomiting, abdominal cramps, body aches, restlessness, irritability, dilated pupils, tremors, involuntary twitching, lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose flesh, or diarrhea

** Printed name for initials: ____ _____ | ____ _____ | ____ _____
Initials Printed name Initials Printed name Initials Printed name

Final Disposition: □Completed treatment □Stopped treatment □ adverse event □ lost to f/u □ moved □ other
Final Disposition Date: _____

UDOH 10/1/12

UTAH DEPARTMENT OF HEALTH DIRECTLY OBSERVED THERAPY LOG

12-Dose Isoniazid-Rifapentine Latent TB Infection Treatment

Patient Name: ______________________________

Laboratory Log

If levels are abnormal, please describe in Comments section. Include abnormal level(s) and action taken.

	Date	Date	Date	Date	Date	Date	Date	Date
LFT	☐normal ☐abnormal ________	☐normal ☐ abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________
CBC	☐normal ☐abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________	☐normal ☐abnormal ________

Adverse Event Episode Log

Please complete for any adverse event which causes interruption in therapy, and notify State TB Nurse Consultant (801)538-9906.

Date	Onset of symptoms	Symptom Duration	Hospitalized	# doses taken	Rechallenge	Outcome
	□ < 2 hrs □ 2-48hrs □ >48hrs	□ < 1 day ___hrs □ > 1 day ___days	□ yes □ no		□ yes □ no	□ continue Rx □ INH intolerant □RPT intolerant
	□ < 2 hrs □ 2-48hrs □ >48hrs	□ < 1 day ___hrs □ > 1 day ___days	□ yes □ no		□ yes □ no	□ continue Rx □ INH intolerant □RPT intolerant
	□ < 2 hrs □ 2-48hrs □ >48hrs	□ < 1 day ___hrs □ > 1 day ___days	□ yes □ no		□ yes □ no	□ continue Rx □ INH intolerant □RPT intolerant
	□ < 2 hrs □ 2-48hrs □ >48hrs	□ < 1 day ___hrs □ > 1 day ___days	□ yes □ no		□ yes □ no	□ continue Rx □ INH intolerant □RPT intolerant

Report event requiring hospitalization within one business day.

Comments

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